Management of *Helicobacter Pylori* Infection
2024 Myanmar Consensus Report

2024

FOREWORD

Developing clinical practice guidelines for clinicians and physicians practicing gastroenterology and hepatology is one of the goals of the Myanmar GI and Liver Society (MGLS), with the aim of enhancing the standard of treatment.

In Myanmar, *Helicobacter pylori (H. pylori)* infection is widespread and continues to rise in tandem with antibiotic resistance. Due to the significant risk of gastric cancer, it is critical to minimize antibiotic resistance while curing the infection.

It is the fruit of intense cooperative effort of experienced gastroenterologists from throughout the nation, considering the cost effectiveness, applicability, and general condition of health care centers in Myanmar.

This compilation of statements serves as the first national guideline for *H. pylori* infection in Myanmar. It addresses indications, diagnosis techniques, the right combination of antibiotics, and treatment duration to combat antibiotic resistance.

I believe this consensus guideline helps clinicians in understanding, diagnosing and treating *H. pylori* infection in daily clinical practice in Myanmar.

Than Than Aye
President
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List of Abbreviations

	Definition
ASA	Acetylsalicylic acid
BQT	Bismuth quadruple therapy
EIA	Enzyme immunoassay
ESD	Endoscopic submucosal dissection
H. pylori	*Helicobacter pylori*
ICA	Immunochromatographic assay
IDA	Iron deficiency anaemia
ITP	Immune thrombocytopenia
ITT	Intention to treat
MALT	Mucosa-associated lymphoid tissue
MGLS	Myanmar GI and Liver Society
NBQT	Non-bismuth quadruple therapy
NCCN	National Comprehensive Cancer Network
NSAID	Non-steroidal anti-inflammatory drugs
P-CABs	Potassium-competitive acid blockers
PCRs	Polymerase chain reactions
PPIs	Proton pump inhibitors
PUD	Peptic ulcer disease
RUT	Rapid urease test
SAT	Stool antigen test
UBT	Urea breath test

Introduction

Myanmar is a country with a high prevalence of *Helicobacter pylori (H. pylori)* infection in Southeast Asia.[1,2,3] *H. pylori* infection causes progressive injury to the gastric mucosa and plays an important role in gastrointestinal diseases such as asymptomatic chronic gastritis, peptic ulcer disease, atrophic gastritis, intestinal metaplasia, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma.[4,5,6,7]

Myanmar has an intermediate risk of gastric cancer because the predominant *H. pylori* strains are Western-type CagA and BabA.[3] According to Globocan 2022, the standardized incidence of gastric cancer in Myanmar is 11.8 per 100,000 people, accounting for 10.5% of all cancer deaths, and is the third leading cause of cancer death in Myanmar.[8]

Multiple antibiotic regimens with antisecretory agents are used for effective eradication. A high bacterial load, high gastric acidity, high virulence of *Helicobacter* strains and poor compliance are associated with unsuccessful eradication. Moreover, increasing antibiotic resistance seems to be the major cause of the decreasing eradication rate.[9] In view of increasing drug resistance in Myanmar, standard management guideline is needed for the effective management of *H. pylori* infection. This is the first consensus guideline in Myanmar for local clinical practice.

These consensus recommendations are based upon the best available evidence from the world's literature and guidelines, with special attention given to evidence from Myanmar. This consensus provides recommendations for *H. pylori* diagnosis and treatment.

Methods

This consensus was initiated by expert gastroenterologists from the University of Medicine, Mandalay. The working groups consisted of 37 gastroenterologists and clinicians from Myanmar GI & Liver Society (MGLS), who had discussions in integrated meetings and developed consensus statements, grades of recommendations, levels of evidence, and rationales for the diagnosis and management of *H. pylori* infection in daily practice in Myanmar. Four areas were discussed: (1) who to test, (2) how to test, (3) who to treat, and (4) how to treat. The consensus process consisted of a series of virtual and physical meetings that were held among panel members from August 2023 to July 2024.

The current knowledge, clinical practice evidence, published guidelines, and journals were collected, investigated, and analysed by working groups. Each section of the guideline was allocated at least one lead author responsible for performing a comprehensive literature search. The working group on each subtopic constructed statements and rationales on the basis of their expertise, and prepared a draft. Whenever possible, guidelines were based on the highest levels of evidence available. If there was no high-quality studies or clear evidence, the guidelines were based on the majority of the consensus advice of expert opinion in the literature and of the writing committee.

The drafted statements and supporting evidence were revised by core members and circulated to all panel members. All the recommendations achieved complete consensus following extensive review and discussion among the guideline development group. The Delphi method was used to develop a consensus. The final draft was reviewed by international expert; Professor Ang Tiing Leong (Changi General Hospital, Singapore) and Associate Professor Duc T. Quach (University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam).

This consensus was developed following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).[10] The recommendation grades were also developed considering the cost effectiveness, applicability, and general condition of health care centers in Myanmar. The considerations were then discussed, and the recommendation grades were determined upon agreement among the experts. All statements and rationales were discussed, and all participants agreed upon the meeting.

All panel members graded the level of evidence, and evaluated the level of agreement and the strength of the recommendations for all statements on the basis of the GRADE system as follows:

- High quality — Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality— Further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate.
- Low quality— Further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality— Any estimate of effect is very uncertain.

With respect to the level of consensus, voting by each faculty member was performed anonymously through an electronic system. Each member will choose one of the following three levels: (1) agree strongly, (2) agree with reservations and (3) disagree. A consensus was achieved when at least 80% of the participants agreed. The voting members were requested to explain the reasons for the votes that were not at level 1 or 2.

The strength of the recommendations was rated on three levels: strong, weak and conditional. Statements that received ≥80% of the votes were considered strong if the quality of evidence was high or moderate and conditional if the quality of evidence was low or very low, and the remaining statements were considered weak. Second round voting of the statements which did not have strong agreement to achieve maximum consensus was made two weeks after first voting via zoom platform. All final approved statements, level of evidence and grade of recommendation are summarized in Table 1.

Table 1: Recommendation Statements, Level of Evidence and Grade of Recommendation

Statement	Recommendations	Level of Evidence	Grade of Recommendation
Who to Test			
1	Patients with uninvestigated dyspepsia are advised to test for *H. pylori* infection.	High	Strong (96%)
2	All patients with dyspepsia who undergo upper gastrointestinal endoscopy should be tested for *H. pylori* infection by a biopsy-based method, even with normal endoscopic findings.	High	Strong (90%)
3	All patients with endoscopically proven any stage of peptic ulcer or previous history of peptic ulcer disease (PUD) should be tested for *H. pylori* infection.	High	Strong (94%)
4	All patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma should be tested for *H. pylori* infection.	High	Strong (100%)
5	All patients with a history of endoscopic resection or subtotal gastrectomy for early gastric cancer should be tested for *H. pylori* infection.	High	Strong (90%)
6	It is advisable to test *H. pylori* infection in patients taking long-term low-dose aspirin (acetylsalicylic acid).	High	Strong (84%)
7	Patients who need long-term non-steroidal anti-inflammatory drugs (NSAID) therapy should be tested for *H. pylor*i infection.	High	Strong (94%)
8	Patients with unexplained iron deficiency anaemia (IDA) after adequate evaluation should be tested for *H. pylori* infection.	High	Strong (93%)

9.	All adult patients with immune thrombocytopenia (ITP) should be tested for *H. pylori* infection.	High	Strong (93%)
10.	*H. pylori* should be tested in persons who had a family history of gastric cancer in first-degree relatives.	High	Strong (87%)
How to test			
11	The urea breath test (UBT) is the recommended non-invasive method to detect active *H. pylori* infection.	High	Strong (97%)
12	Monoclonal stool antigen test (SAT) is an alternative test for detection of active *H. pylori* infection.	High	Strong (84%)
13	Serology tests should not be used for detection of active *H. pylori* infection.	High	Strong (97%)
14	The rapid urease test (RUT) is the recommended test to detect *H. pylori* in clinical practice when there is an indication for endoscopy.	Moderate	Strong (94%)
15	Culture or molecular biology is not recommended for routine diagnosis of *H. pylori* infection.	Moderate	Strong (94%)
16	For detecting *H. pylori* infection, proton pump inhibitors (PPIs) should be discontinued for at least 2 weeks and antibiotics or bismuth compounds should be discontinued for at least 4 weeks before the test.	High	Strong (97%)
Who to treat			
17	*H. pylori* eradication therapy is recommended to all patients who test positive for active *H. pylori* infection, unless there are competing considerations.	High	Strong (94%)
How to treat			
18	Duration of *H. pylori* treatment is recommended for 14 days to maximize the effect.	High	Strong (100%)
19	In *H. pylori* treatment, combined antibiotics pill in suboptimal dosage should not be used.	Low	Strong (94%)

20	In *H. pylori* treatment, high-dose proton pump inhibitors (PPI) twice daily are recommended to improve the efficacy of the therapies.	High	Strong (93%)
21	The recommended first-line (initial) therapies are		
	(a) Non-bismuth quadruple therapy (NBQT)/ concomitant quadruple therapy	High	Strong (90%)
	(b) Bismuth quadruple therapy (BQT)	High	Strong (85%)
21 (a)	Non-bismuth quadruple therapy (NBQT)/ concomitant quadruple therapy is recommended as first-line (initial) therapy for *H. pylori* eradication.	High	Strong (90%)
21 (b)	Bismuth quadruple therapy (BQT) is recommended as first-line (initial) therapy for *H. pylori* eradication.	High	Strong (85%)
22	In patients with *H. pylori* infection, the use of PPI-based triple therapy should be restricted.	High	Strong (83%)
23	In case of initial treatment failure, subsequent therapies (second-line therapies) should be considered.	High	Strong (97%)
23 (a)	After failure of non-bismuth quadruple therapy (NBQT), bismuth quadruple therapy (BQT) is recommended.	High	Strong (97%)
23 (b)	After failure of bismuth quadruple therapy (BQT), non-bismuth quadruple therapy (NBQT) or levofloxacin-containing bismuth quadruple therapy (PPI, levofloxacin, amoxicillin and bismuth) can be subsequent treatment options.	High	Strong (97%)
24	Vonoprazan (potassium-competitive acid blocker) could be potential alternative to PPI if it is available.	High	Strong (93%)
25	Further assessment and antibiotic susceptibility test are recommended for patients who fail second-line therapy.	High	Strong (92%)
26	It is recommended to confirm successful *H. pylori* eradication after therapy. Urea breath test (UBT) is the best option and validated monoclonal stool antigen test (SAT) is an alternative depending upon availability.	High	Strong (94%)

Who to Test

Statement 1: Patients with uninvestigated dyspepsia are advised to test for *H. pylori* infection.

Level of evidence: High

Grade of recommendation: Strong (96%)

Rationale

Myanmar has a high prevalence of *H. pylori* infection, at 67.7% in the asymptomatic population[11] and 48% in dyspeptic patients[12], and *H. pylori* infection is a major risk factor for peptic ulcer disease (PUD), as well as gastric malignancies[11]. The Maastricht VI/ Florence consensus report stated that a test-and-treat strategy will cure most cases of underlying PUD and prevent serious consequences of gastroduodenal diseases associated with *H. pylori* gastritis.[13] Furthermore, eradication therapy benefits patients with *H. pylori* infection-associated non-ulcer dyspepsia.[13] There was a small but statistically significant reduction in subsequent consultations at the primary care level for dyspeptic complaints after testing and treating *H. pylori* infection.[14]

Statement 2: All patients with dyspepsia who undergo upper gastrointestinal endoscopy should be tested for *H. pylori* infection by a biopsy-based method, even with normal endoscopic findings.

Level of evidence: High

Grade of recommendation: Strong (90%)

Rationale

H. pylori infection is one of the causes of dyspepsia and a major risk factor for gastric malignancy. *H. pylori* eradication provides cumulative long-term benefits in infected individuals with dyspepsia.[14] Kyoto's global consensus report highlighted that the maximum benefit of *H. pylori* eradication is obtained if it is performed while mucosal damage is still non-atrophic.[15] Therefore, all dyspeptic patients who undergo upper gastrointestinal endoscopy should be tested for *H. pylori* infection.

Statement 3: All patients with endoscopically proven any stage of peptic ulcer or previous history of peptic ulcer disease (PUD) should be tested for *H. pylori* infection.

Level of evidence: High

Grade of recommendation: Strong (94%)

Rationale

The relationship between *H. pylori* and PUD has been well established. Approximately 90% of duodenal ulcers and 70% to 80% of gastric ulcers are caused by *H. pylori* infection and *H. pylori* eradication results in the elimination of peptic ulcers.[14] The estimated lifetime risk of PUD in individuals with *H. pylori* infection is 15–20%.[16] PUD continues to be a very common and important condition that leads to major mortality and morbidity due to pain, bleeding, and perforation.[16] Similarly, *H. pylori*-induced gastritis is considered the most important risk factor for peptic ulcers and their complications as well as for gastric cancer. The risk of peptic ulcer bleeding is almost doubled in patients with *H. pylori* infection[17] and it's eradication markedly reduces recurrent gastrointestinal bleeding in patients with a prior history of gastrointestinal bleeding.[18]

Statement 4: All patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma should be tested for *H. pylori* infection.

Level of evidence: High

Grade of recommendation: Strong (100%)

Rationale

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell neoplasia commonly associated with *H. pylori*-induced chronic gastritis.[19] *H. pylori* infection is the predominant pathogenic mechanism underlying the development of gastric MALT lymphoma.[20] In more than 90% of cases, MALT lymphoma is associated with *H. pylori* infection.[21] Low-grade MALT lymphoma can be cured by *H. pylori* eradication in 60–80% of cases.[22,23,24] *H. pylori* eradication has been recommended as the first-line treatment for low-grade gastric marginal zone lymphoma since 2012.[17] The National Comprehensive Cancer Network (NCCN) recommends *H. pylori* testing as an essential workup for extranodal marginal zone B-cell lymphoma, and *H. pylori* eradication is recommended as initial therapy for *H. pylori*-positive Lugano stages I E to II E.[25]

Statement 5: All patients with a history of endoscopic resection or subtotal gastrectomy for early gastric cancer should be tested for *H. pylori* infection.

Evidence level: High

Grade of recommendation: Strong (90%)

Rationale

The risk of developing metachronous gastric lesions or neoplasia in the remaining gastric mucosa is significant after both endoscopic and surgical resection for early gastric cancer.[26] According to a recent meta-analysis, the pooled 5-year and 10-year cumulative incidence rates of metachronous gastric neoplasia after endoscopic submucosal dissection (ESD) for early gastric cancer were 9.5% and 14.9%, respectively.[27] Furthermore, the reported estimated annual incidence of metachronous gastric neoplasia ranges from 2.4% to 4.7%.[28]

Studies have reported that patients with early gastric cancer who received *H. pylori* treatment had lower rates of metachronous gastric cancer and greater improvement from baseline in the grade of gastric corpus atrophy.[29,30,31] A fifteen- year follow-up study on the survival rate of patients with gastric cancer revealed statistically significant benefits in overall and gastric cancer-specific survival in the eradication group. Therefore, more intensive detection of *H. pylori* infection is recommended in patients who are surgically treated for gastric cancer, regardless of cancer stage.[32] With respect to the timing of *H. pylori* detection after endoscopic resection and surgery, large cohort studies have shown that eradication therapy within one year after gastric cancer treatment reduces the risk of developing metachronous gastric neoplasms compared with late prescription of therapy.[33,34]

Statement 6: It is advisable to test *H. pylori* infection in patients taking long-term low- dose aspirin (acetylsalicylic acid).

Evidence level: High

Grade of recommendation: Strong (84%)

Rationale

Acetylsalicylic acid (ASA) use increases the risk of upper gastrointestinal tract ulcerations. *H. pylori* infection is a recognized risk factor for the development of ulcers and ulcer bleeding during low-dose ASA treatment.[35] Three cohorts of ASA users (160 mg/day) with over 3000 patients were included. *H. pylori* infection was present in 93.33% of patients with bleeding duodenal ulcers, 83.33% with bleeding gastric ulcers and 96.15% with acute mucosal lesions.[19] A meta- analysis reported that *H. pylori* increases the risk of ulcers in almost 70% of low-dose ASA users, even in a

population that is taking acid suppressants.[36] Furthermore, *H. pylori* infection increases the risk of duodenal ulcers, gastric ulcers and acute mucosal bleeding.[37] In patients with a prior history of gastrointestinal bleeding, *H. pylori* eradication markedly reduces recurrent gastrointestinal bleeding.[19] The largest double-blind placebo-controlled randomized trial from the UK (Helicobacter Eradication Aspirin Trial – HEAT) investigated the effects of *H. pylori* eradication on subsequent ulcer bleeding in infected individuals taking ASA daily. There was a significant reduction in the incidence of peptic ulcer bleeding in the active eradication group in the first 2.5 years of follow-up. However, the long-term effects might not be sustainable.[38,39] The Maastricht VI/Florence consensus report advises *H. pylori* testing and treatment in high-risk patients who are already on long-term aspirin.

The high-risk groups of patients include those with advanced age (with those aged > 75 years at particularly increased risk of complications), comorbidities, coprescription of other drugs associated with ulceration and bleeding (ASA, antiplatelet drugs, anticoagulants, corticosteroids and selective serotonin reuptake inhibitors), smoking and past history of PUD or bleeding.[40,41]

Statement 7: Patients who need long-term non-steroidal anti-inflammatory drugs (NSAID) therapy should be tested for *H. pylori* infection.

Evidence level: High

Grade of recommendation: Strong (94%)

Rationale

Both *H. pylori* infection and NSAID use independently and significantly increased the risk of peptic ulcer and ulcer bleeding in most studies. A meta-analysis reported that PUD was significantly more common in *H. pylori* positive patients.[42] Moreover, eradication of *H. pylori* reduces the incidence of PUD and the risk of ulcer bleeding in NSAID users, especially naïve users.[43,44,45] However, international guideline[46] dose not support the testing and treatment of *H. pylori* in all NSAID users because the risk for NSAID-associated ulcer disease varies according to host risk factors and the toxicity of the NSAID used and the duration, dose and frequency of the therapy. *H. pylori* eradication alone is not effective enough to replace PPI maintenance therapy in high-risk patients.[46] The Maastricht VI/Florence consensus report advises *H. pylori* testing and treatment in naïve patients starting long-term NSAID therapy.[13] Those at high-risk may need additional PPI therapy.

Therefore, *H. pylori* eradication is recommended for long-term NSAID users, especially high-risk patients and NSAID-naïve patients.

Statement 8: Patients with unexplained iron deficiency anaemia (IDA) after adequate evaluation should be tested for *H. pylori* infection.

Evidence level: High

Grade of recommendation: Strong (93%)

Rationale

Blecker *et al*. first identified the association between *H. pylori* and IDA in 1991.[47] *H. pylori* colonization may impair iron uptake and increase iron loss, potentially leading to iron deficiency.[48] IDA is more prevalent in *H. pylori*-infected individuals than in *H. pylori*-negative individuals.[49,50] *H. pylori* eradication increased haemoglobin levels in those with moderate to severe anaemia and improved the levels of markers of iron status.[50, 51,52.53] Recent international guidelines[13,40] recommend *H. pylori* detection and eradication therapy in patients with recurrent IDA with normal upper gastrointestinal endoscopy and colonoscopy results.

Statement 9: All adult patients with immune thrombocytopenia (ITP) should be tested for *H. pylori* infection.

Level of evidence: High

Level of recommendation: Strong (93%)

Rationale

The relationship between *H. pylori* and ITP was first described by García Pérez *et al*. in 1993 in Spain.[54] The data from the European continent, Asian continent and North America supported the relationship of *H. pylori* with ITP and platelet recovery after *H. pylori* eradication.[55,56]

A systematic review of 25 studies on 1555 adult patients revealed that platelet counts in ITP patients tended to increase after *H. pylori* eradication.[57] A meta-analysis including six studies by a Korean group and recent studies from the Middle East, indicated that *H. pylori* eradication has a significant therapeutic effect on patients with ITP.[58, 59]

In Myanmar, three descriptive studies involving patients with adult ITP and *H. pylori* infection using different diagnostic tools (serology and stool antigen tests) have been conducted, but a significant association between *H. pylori* infection and ITP was found in only one local study. Among the 73 immune and non-immune thrombocytopenic patients, 59% were *H. pylori* positive.[60,61,62] The Maastricht IV/Florence consensus report recommend testing for *H. pylori* infection in all adult patients with ITP.[17]

Statement 10: *H. pylori* should be tested in persons who had a family history of gastric cancer in first- degree relatives.

Level of evidence: High

Level of recommendation: Strong (87%)

Rationale

The international agency for research on cancer declared *H. pylori* to be a group I human carcinogen for gastric adenocarcinoma.[63] A family history of gastric cancer in a first-degree relative is associated with a double to triple the risk of gastric cancer.[64] In the meta-analysis, first-degree relatives of patients with gastric cancer had a significantly greater risk of harboring *H. pylori* and a greater risk of developing the precancerous lesions of atrophy and intestinal metaplasia.[65]

The largest prospective studies on family history and gastric cancer in both Asian[66] and Western populations[67] revealed that the risk of incident gastric cancer was greater in individuals with a family history of gastric cancer. Moreover, *H. pylori* eradication treatment reduces the risk of gastric cancer among first-degree relatives with *H. pylori* infection who have a family history of gastric cancer.[68,69] Genetic predispositions or shared exposure to common environmental factors, including carcinogenic *H. pylor*i strains, shared dietary habits, or other factors that promote cancer development, may explain these associations.[66]

Maastricht V[70] and the Bangkok[71] consensus report strongly recommend testing for *H. pylori* infection in the first-degree relatives of patients with gastric cancer to reduce the risk of gastric cancer among family members.

How to Test

H. pylori infection is diagnosed using non-invasive tests and invasive tests. Non-invasive tests include urea breath test (UBT), stool antigen test (SAT) and *H. pylori* antibody serological tests, whereas invasive tests include rapid urease test (RUT), histopathology examinations, tissue culture, sensitivity tests and polymerase chain reactions (PCRs).

Statement 11: The urea breath test (UBT) is the recommended non-invasive method to detect active *H. pylori* infection.

Level of Evidence: High

Grade of recommendation: Strong (97%)

Rationale

The urea breath test (UBT) includes 13C-UBT and 14C-UBT. It is the most frequently used non-invasive test.[72] It has the advantages of high accuracy of *H. pylori* detection, is easy to perform and is not influenced by the focal distribution of *H. pylori* in the stomach. In people without a history of gastrectomy and those who have not recently received antibiotics or proton pump inhibitors (PPI), UBT has the highest diagnostic accuracy. The sensitivity of *H. pylori* testing, given its prevalence of 53.7% and specificity of 0.9%, is 94% for UBT and 83% for SAT.[73]

However, the accuracy of this method decreases significantly in patients who have undergone partial gastrectomy, and other tests, such as RUT and/or histological methods, should be replaced under these conditions.[74] The cost of UBT is higher than that of SAT. Moreover, it is not available countrywide.

Statement 12: Monoclonal stool antigen test (SAT) is an alternative test for detection of active *H. pylori* infection.

Level of Evidence: High

Grade of recommendation: Strong (84%)

Rationale

SATs are relatively inexpensive, non-invasive tests that are useful in developing countries.[75] SATs are available in 2 formats: (a) laboratory tests based on enzyme immunoassay (EIA) and (b) rapid in-office tests using an immunochromatographic assay (ICA) technique. A meta- analysis of 22 studies including 2499 patients revealed that the diagnostic accuracy of the stool antigen test (SAT) is equivalent to that of the UBT if a validated laboratory-based monoclonal test is used.[76]

SATs have advantages for detecting *H. pylori* in patients with poor compliance (such as children) for UBT. The laboratory-based monoclonal stool antigen test (EIA) is preferred because the currently available ICA-based tests provide less reliable results, although they are fast and easy to use.[77] Furthermore, there are currently no locally validated ICA-based tests in Myanmar. If available, the monoclonal stool antigen test is an alternative non-invasive test.

Statement 13: Serology tests should not be used for detection of active *H. pylori* infection.

Level of Evidence: High

Grade of recommendation: Strong (97%)

Rationale

Although the overall sensitivity of commercial serological kits for *H. pylori* infection is 85%, positive results may not reflect current *H. pylori* infection. The main issues with current serological tests are decreased sensitivity compared with other non-invasive methods, and the inability to distinguish between past and active infections.[78] Therefore, serological tests are not useful for confirming eradication after treatment.

Statement 14: The rapid urease test (RUT) is the recommended test to detect *H. pylori* in clinical practice when there is an indication for endoscopy.

Level of Evidence: Moderate

Grade of recommendation: Strong (94%)

Rationale

The RUT has the advantages of being a rapid and simple test with relatively high accuracy with sensitivity (88%–93%) and specificity (99%), providing a quick result after endoscopy.[79] The distribution of *H. pylori* is patchy in the stomach, and biopsy from multiple sites can improve the accuracy of detection. Therefore, at least two biopsies should be obtained from the antrum and corpus. The sensitivity and negative predictive value of the RUT are lower in patients presenting with upper gastrointestinal bleeding (54.5% vs. 73%).[80] After eradication therapy, the *H. pylori* density decreases, and its distribution in the stomach is altered, which may lead to false-negative test results. Therefore, RUT is not usually recommended for the detection of *H. pylori* after eradication therapy.[81]

Statement 15: Culture or molecular biology is not recommended for routine diagnosis of *H. pylori* infection.

Evidence level: Moderate

Strength of recommendation: Strong (94%)

Rationale

SAT and UBT for *H. pylori* have high sensitivity and specificity[82] and these tests are easily available and easy to perform. The culture method needs technical requirements and has relatively low sensitivity for detecting *H. pylori* despite high specificity (100%).[83] Cultured *H. pylori* strains can be used for susceptibility tests and bacteriology studies.[84,85] Moreover, molecular biology technology is currently practical for detecting *H. pylori* resistance gene mutations and for predicting drug resistance.[86] It can be recommended in cases of *H. pylori* infection treatment failure.[84,87] It is used only for research purposes in Myanmar and is not available in routine clinical practice.

Statement 16: For detecting *H. pylori* infection, proton pump inhibitors (PPIs) should be discontinued for at least 2 weeks and antibiotics or bismuth compounds should be discontinued for at least 4 weeks before the test.

Evidence level: High

Strength of recommendation: Strong (97%)

Rationale

Antimicrobials and bismuth can inhibit the growth of *H. pylori* and reduce its activity. PPIs inhibit the secretion of gastric acid, leading to a significant increase in the gastric pH, which influences *H. pylori* urease activity.[88, 89] These drugs may significantly influence the results of *H. pylori* assessment because the RUT and UBT are based on urease activity, which can lead to false-negative results.[90] H2 receptor antagonists have a slight effect on the test results, whereas antacids have no obvious effect.[91] Serology tests for detecting *H. pylori* antibodies and molecular biology methods for detecting the *H. pylori* gene are not affected by these drugs.[92, 93] Guidelines recommend discontinuing PPIs 2 weeks prior to *H. pylori* testing and discontinuing antibiotics, including bismuth 4 weeks prior to testing for initial diagnosis and confirmation of eradication.[94]

Who to Treat

Statement 17: *H. pylori* eradication therapy is recommended to all patients who test positive for active *H. pylori* infection, unless there are competing considerations.

Level of Evidence: High

Grade of recommendation: Strong (94%)

Rationale

Since all patients with a positive test for active infection with *H. pylori* should be offered treatment,[16] the critical issue is which patients should be tested for infection. These issues have already been mentioned in the "who to test" session.

Although there are structural and functional abnormalities due to chronic active inflammation, a majority of patients have no apparent clinical symptoms.[16,95] Eradication therapy restores normal gastric mucosa or halts progression to mucosal lesions and can reduce symptoms, minimize complications of infection and reduce gastric cancer risk.[95,96,97,98,99,100,101,102,103,104,105,106,107]

For the community, the additional benefit includes the prevention of infection transmission to others. International guidelines recommend the eradication of *H. pylori* infection even in the absence of symptoms,[16,70,108] although there is only a negligible negative impact of eradication therapies on human health, such as an increase in allergies or obesity and perturbation of the microbiota.[109,110]

How to Treat

The duration and regime of eradication therapies are recommended depending on local successful eradication rates, pathogen susceptibility and resistance profiles, and drug availability. The statements in this section were developed on the basis of available local and international drug sensitivity profiles and regimens.

Statement 18: Duration of *H. pylori* treatment is recommended for 14 days to maximize the effect.

Level of evidence: High

Grade of recommendation: Strong (100%)

Rationale

The optimum duration of therapy is defined as days of therapy required to reliably achieve 95% or greater cure rates in adherent patients with susceptible *H. pylori* infection.[111] With respect to concomitant quadruple therapy, the eradication rates are higher with 14-day than with 10-day therapy[112,113]

For bismuth quadruple therapy (BQT), when given for 10–14 days, the eradication rate reached 90–100% in the presence of clarithromycin resistance and reached a ≥85% eradication rate even in areas with a high prevalence of metronidazole resistance.[114] Although there was no statistically significant difference between the eradication rates at 10 days and 14 days in a recent meta-analysis,[115] a local study reported that the eradication rate was 92% after 14 days of BQT.[116]

The most recent World Gastroenterology Organization global guideline recommend that the duration of *H. pylori* eradication treatment should be 14 days unless there is local evidence of equally effective eradication therapy with a shorter duration.[117] Given the unavailability of susceptibility tests and high metronidazole resistance in Myanmar, 14-day BQT is suitable for improving the eradication of *H. pylori* infection.

Statement 19: In *H. pylori* treatment, combined antibiotics pill in suboptimal dosage should not be used.

Level of evidence: Low

Grade of recommendation: Strong (94%)

Rationale

Commercially available fixed-dose PPI-based triple therapies (treatment kits) involve different combinations of suboptimal doses of antibiotics and PPIs. In addition, the efficacy of standard triple therapy is decreasing. Therefore, it is important to select antibiotics and PPIs at optimal doses to prevent antibiotic resistance.

Statement 20: In *H. pylori* treatment, high-dose proton pump inhibitors (PPI) twice daily are recommended to improve the efficacy of the therapies.

Level of evidence: High

Grade of recommendation: Strong (93%)

Rationale

The effectiveness of PPI therapy is related to the dose, frequency of administration, CYP2C19 polymorphism status and presence and severity of corpus gastritis in patients.[118,119,120] Bacteria enter the replicative state and become susceptible to antibiotics when the gastric pH is high.[121] Therefore, to increase the *H. pylori* eradication rate, the antisecretory effect of PPIs should be optimized. High-dose PPI refers to 40 mg of omeprazole (that is, a double dose), or an equivalent (if other PPIs are prescribed) (Table 2).[113,122,123] Different PPIs can be used interchangeably and cost effectively on the basis of their omeprazole equivalency.[113,124]

Table 2: Dosage of High-Dose Proton Pump Inhibitors

Proton pump inhibitors	Dosage
Rabeprazole	20 mg BID
Esomeprazole	20 mg BID
Lanzoprazole	45 mg BID
Omeprazole	40 mg BID
Pantoprazole	120 mg BID

Statement 21: The recommended first-line (initial) therapies are
(a) Non-bismuth quadruple therapy (NBQT)/concomitant quadruple therapy
(b) Bismuth quadruple therapy (BQT)

Statement 21(a): Non-bismuth quadruple therapy is recommended as first-line (initial) therapy for *H. pylori* eradication.

Level of Evidence: High

Grade of recommendation: Strong (90%)

Rationale

NBQT/concomitant quadruple therapy consists of high-dose PPI BID, amoxicillin 1 g BID, metronidazole 500 mg BID/Tinidazole 500 mg BID and clarithromycin 500 mg BID for

14 days (Table 3).

Metronidazole 500 mg is not available in Myanmar. Local study have shown that tinidazole 500 mg BID has similar efficacy (Intention to treat (ITT) 84.09% in the tinidazole group vs 88% in the metronidazole group).[125]

Systematic reviews and meta-analysis have shown that NBQT has high efficacy, with an eradication rate of over 90% , which is superior to that of clarithromycin containing standard triple and sequential therapy.[126,127,128] A prospective non-inferiority multicenter trial showed similar outcomes: NBQT cured more than 90% of patients with *H. pylori* infections, even in areas with high clarithromycin and metronidazole resistance.[129] The Toronto Consensus recommend that concomitant quadruple therapy for 14 days be considered a first-line option.[130]

Hp-EuReg reported that concomitant quadruple therapy was the only therapy other than BQT that consistently achieved >90% eradication success.[113] Furthermore, NBQT had better efficacy after vonoprazan-triple therapy among different first-line treatment regimens for *H. pylori* infection according to a recent network meta-analysis.[131] Three local studies that used 14 days of NBQT as a first-line therapy reported eradication rates of 93%[132,] 88%[116] and 84.09%[125] respectively for ITTs.

The Maastricht VI/Florence consensus report stated that NBQT may be considered first -line therapy when BQT is not available.[13] However, the Bangkok consensus stated that clarithromycin should not be prescribed to patients with known or highly suspected resistance to clarithromycin (e.g., after failure of clarithromycin triple therapy). Again, quadruple therapies are generally reserved for use as empiric therapies in situations where dual resistance (e.g, clarithromycin–metronidazole) is known to be low.[71] Myanmar has high metronidazole resistance and low eradication with triple therapy containing clarithromycin; therefore, the use of NBQT with caution, e.g., a careful history of clarithromycin exposure and a history of failure of triple therapy with clarithromycin, is recommended.

Statement 21(b): Bismuth quadruple therapy (BQT) is recomended as first-line (initial) therapy for *H. pylori* eradication.

Level of evidence: High

Grade of recommendation: Strong (85%)

Rationale

BQT consists of bismuth subsalicylate 524 mg QID or bismuth subcitrate 240 mg BID, metronidazole 500 mg TID, tetracycline 500 mg QID and high-dose PPI BID for 14 days (Table 3).

BQT overcomes clarithromycin resistance, and its efficacy is not affected by metronidazole resistance.[133] The major effect of bismuth is to add an additional 30–40% to the success rate of resistant infections.[134]

The primary eradication rates of clarithromycin- and metronidazole-containing standard triple therapy have significantly decreased in Myanmar. Although the eradication rate has varied across different local studies, most of the data have not reached a successful eradication level (< 80%).[11.132, 135,136,137,138] The Maastricht VI/Florence consensus report stated that BQT is the first-line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance if individual susceptibility testing is not available.[13]

The rate of BQT eradication worldwide is > 90% for both first- and second-line therapies.[113.139,140,141] Compared with concomitant quadruple therapy, BQT has similar efficacy and safety profiles in areas with high clarithromycin resistance.[142] A recent systematic review and meta-analysis revealed that the eradication rate of BQT was comparable to that of concomitant quadruple therapy (87.4% vs 85.2%).[143] The eradication rate of BQT was 85.3% (ITT), which was 92.5% in a local study (per protocol).[116]

The adverse effects of BQT, such as nausea, diarrhea, fatigue, metallic taste, abdominal pain, dark or black stool, and blackening of the tongue, can affect compliance. However, the adverse event rate of BQT was similar to that of nonbismuth quadruple therapy. Its high cost and pill burden (high number of pills) or complicated dosage can also be associated with poor compliance.[144]

BQT is also recommended as first-line (initial) therapy in patients who are allergic to penicillin and/or who have a history of macrolide exposure for more than 2 weeks.[145] Because of its excellent eradication rate and similar adverse event rates to those of NBQT, it is recommended as a first-line therapy.

Statement 22: In patients with *H.pylori* infection, the use of PPI-based triple therapy should be restricted.

Level of Evidence: High

Grade of recommendation: Strong (83%)

Rationale

Standard triple therapy consists of amoxicillin 1 g BID, clarithromycin 500 mg BID and PPI BID for 14 days.

The major determinant of eradication success with this combination is pretreatment resistance to clarithromycin.[117] A high prevalence of clarithromycin resistance results in a

high rate of eradication failure. In Myanmar, clarithromycin is easily available and has been commonly used as monotherapy for other infections, such as respiratory tract infections; hence, clarithromycin resistance is often high and increasing.

Local susceptibility data revealed that the degree of resistance to clarithromycin was high at 63.6%.[146] The primary eradication rates of clarithromycin- and metronidazole-containing standard triple therapy have significantly decreased.

The eradication rate of clarithromycin containing standard triple therapy in asymptomatic monks (outside the hospital setting) was 66.7%[11] more than a decade ago. Although the eradication rate varies across different local studies, most of the data do not indicate successful eradication (<80%), i.e. 64%[135] and 43%[136] In a recent network meta-analysis, the standard triple therapy had an eradication rate of 75.7%, and it was the least efficacious regimen (74.9– 76.44%) comparing among multiple different first-line treatment regimens for *H. pylori* infection.[131] It is therefore advisable to restrict the use of triple therapy (both metronidazole- and clarithromycin-containing triple therapy) as the first-line *H. pylori* eradication treatment. A recent study revealed that clarithromycin-containing triple therapy for *H. pylori* eradication induces increased long-term resistant bacterial communities in the gut.[147] Therefore, this study suggested the restricted use of PPI-based triple therapy.

Statement 23: In case of initial treatment failure, subsequent therapies (second-line therapies) should be considered.

(a) After failure of non-bismuth quadruple therapy (NBQT), bismuth quadruple therapy (BQT) is recommended.

(b) After failure of bismuth quadruple therapy (BQT), non-bismuth quadruple therapy (NBQT) or levofloxacin-containing bismuth quadruple therapy (PPI, levofloxacin, amoxicillin and bismuth) can be subsequent treatment options.

Level of Evidence: High

Grade of recommendation: Strong (97%)

Statement 23(a): After failure of non-bismuth quadruple therapy (NBQT), bismuth quadruple therapy (BQT) is recommended.

Rationale

Bismuth has a synergistic effect with antibiotics and overcomes clarithromycin and levofloxacin resistance. Metronidazole resistance does not affect eradication results in clinical practice if the antibiotic is used at a dosage of ≥1,500 mg/day in combination with bismuth.[148] A meta-analysis revealed that 10 days of treatment with BQT achieved an effective eradication

rate of approximately 90% for both first- and second-line therapy.[149] In a local study, a 14 days of treatment with BQT with 1200 mg of metronidazole resulted in a 92% eradicationrate as first-line therapy.[116] This regimen is also suitable for patients who are allergic to penicillin.

Statement 23(b): After failure of bismuth quadruple therapy (BQT), non-bismuth quadruple therapy (NBQT) or levofloxacin-containing bismuth quadruple therapy (PPI, levofloxacin, amoxicillin and bismuth) can be subsequent treatment options.

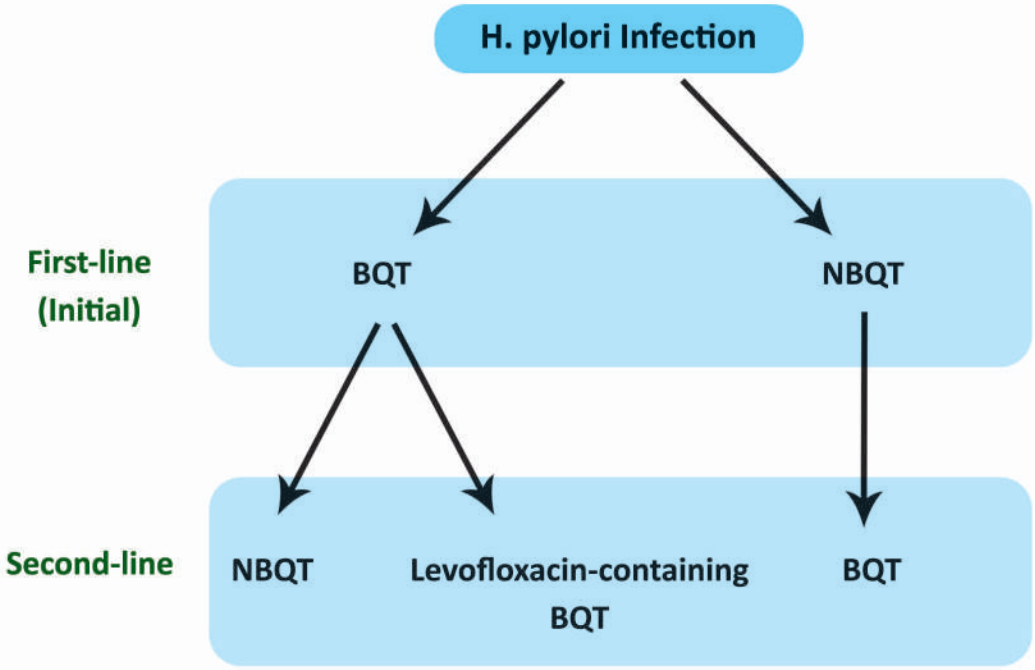
Rationale

After failure of BQT as a first-line therapy, levofloxacin-containing bismuth quadruple therapy has been shown to be useful (Table 3). Previous studies reported that the eradication rate of the levofloxacin triple regimen improved when bismuth was added.[134] The caveat is that there has been increasing fluoroquinolone resistance in Myanmar. Fluoroquinolone-resistant Enterobacteriaceae were found in 88.6% of blood samples from febrile patients from tertiary hospitals in large cities.[150] According to local data, the rate of levofloxacin-containing triple therapy in dyspeptic patients was only 50.8%.[136] This was the only study in Myanmar regarding the levofloxacin regimen. This seems to increase quinolone resistance in Myanmar. There are no data on levofloxacin-containing quadruple therapy (i.e., PPI, levofloxacin, amoxicillin and bismuth) in Myanmar.

High-dose dual therapy (amoxicillin and PPIs for 14 days) might be an alternative option. However, a single-center study with a relatively small sample size in Myanmar revealed that the eradication rate with high-dose dual therapy was only 69%.[151]

Vonoprazan-containing triple therapy is promising in other countries. However, it is not yet available in Myanmar. Rifabutin-based triple therapy should not be used in countries where tuberculosis is prevalent.[117]

Patients who fail second-line treatment despite good adherence are recommended to refer gastroenterologists.


H. pylori Infection
First-line
(Initial)
BQT
NBQT
Second-line
NBQT
Levofloxacin-containing
BQT
BQT

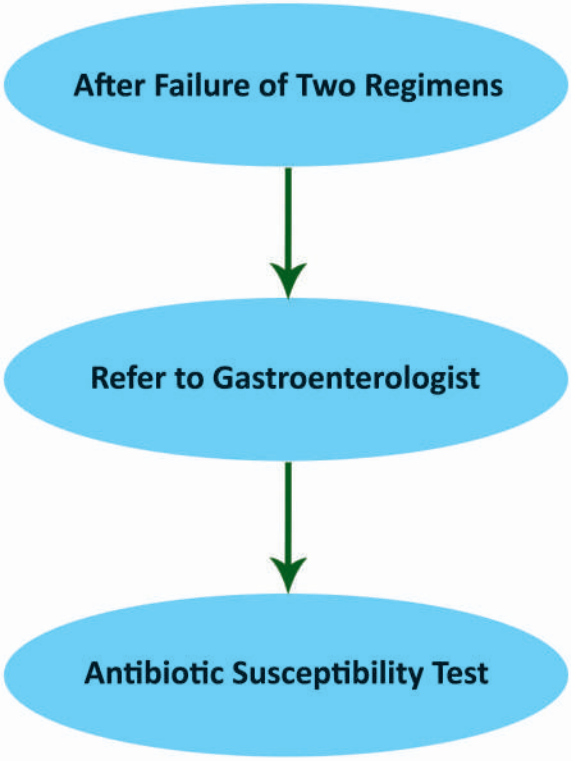

After Failure of Two Regimens
Refer to Gastroenterologist
Antibiotic Susceptibility Test

Table 3: H.pylori Eradication Therapy

First-Line (Initial) Therapy

Non-bismuth Quadruple Therapy (Concomitant Quadruple Therapy)	**Dosage**	**Duration**
Amoxicillin	1 g BID	14 days
Clarithromycin	500 mg BID	14 days
Tinidazole/Metronidazole*	500 mg BID	14 days
PPI (Table 2)	BID	14 days

Bismuth Quadruple Therapy	**Dosage**	**Duration**
Bismuth Subsalicylate	524 mg QID	14 days
Tetracycline	500 mg QID	14 days
Metronidazole*	500 mg TID	14 days
PPI (Table 2)	BID	14 days

Second-line therapy

Levofloxacin-Containing Bismuth Quadruple Therapy	**Dosage**	**Duration**
Levofloxacin	500 mg OD	14 days
Bismuth subsalicylate	524 mg QID	14 days
Amoxicillin	1 g BID	14 days
PPI (Table 2)	BID	14 days

**** Metronidazole available in Myanmar - 200 mg***

Statement 24: Vonoprazan (potassium-competitive acid blocker) could be potential alternative to PPI if it is available.

Level of Evidence: High

Grade of recommendation: Strong (93%)

Rationale

The mechanism of action of potassium-competitive acid blockers (P-CABs) is different from that of PPIs. P-CABs are highly active drugs that target H+/K+ ATPase during gastric acid secretion by parietal cells. Conventional PPIs require 3-5 days to achieve maximal and steady-state gastric acid inhibition, whereas P-CABs increase the intragastric pH to nearly 7 within 4 hours.[152] The novel P-CAB vonoprazan (VPZ) exerts a rapid and sustained suppressive effect on gastric acid for optimal *H. pylori* treatment.[153] Many RCTs and systematic reviews and meta-analyses have reported that *H. pylori* eradication with a VPZ-based regimen is more useful than with PPI-based triple therapy as a first-line *H. pylori* eradication therapy.[154,155,156,157,158] A recent systematic review and meta-analysis revealed that *H. pylori* eradication with VPZ and amoxicillin dual therapy was noninferior to that with VPZ-based triple therapy.[159] There are no data concerning the use of a VPZ-containing regimen in Myanmar, as it is not available in the market. However, VPZ-based *H. pylori* eradication should be conducted in future research. Comparing different types of PCAB, systemic review and recent meta-analysis[160] showed VPZ has the best eradication rate and superior ulcer healing rates compared to keverprazan and tegoprazan. In terms of safety, keverprazan is better than VPZ.

Statement 25: Further assessment and antibiotic susceptibility test are recommended for patients who fail second-line therapy.

Level of Evidence: High

Grade of recommendation: Strong (92%)

Rationale

Antibiotic resistance is the most important factor responsible for treatment failure. NBQT has a significant effect on dual resistance.[161] Although the systematic review and meta-analysis of susceptibility-guided triple therapies have proven more effective than empirical triple therapies in first-line treatment,[162,163] routine tests for antibiotic susceptibility are not feasible because of the low availability of resources. Referral to a specialist is recommended for patients who fail second-line treatment despite good adherence to the drugs.

Statement 26: It is recommended to confirm successful *H. pylori* eradication after therapy. Urea breath test (UBT) is the best option and validated monoclonal stool antigen test (SAT) is an alternative depending upon availability.

Level of evidence: High

Grade of recommendation: strong (94%)

Rationale

Currently, the eradication rate of *H. pylori* is markedly decreasing, and patients who do not achieve eradication are still at risk of suffering serious complications. Therefore, it is recommended that *H. pylori* eradication be confirmed in all patients after therapy.[164,165] The test should be performed at least 4 weeks after the completion of therapy.

Most patients do not require endoscopy after *H. pylori* eradication therapy. Although a non-invasive method, UBT (sensitivity of 96%, specificity of 93%) is the test of choice,[166,167] a meta-analysis revealed that the diagnostic accuracy of the stool antigen test (SAT) is equivalent to that of the UBT if a validated laboratory-based monoclonal test is used.[76]

A meta-analysis of five RCTs revealed comparable sensitivity and specificity of UBTs and stool antigen tests in the detection of *H. pylori* eradication after treatment.[168]

Among these two tests, the SAT is easier to conduct, has a lower cost, and is easily available across the country. The Maastricht V[70] and Bangkok[71] consensuses recommend the SAT as an alternative test.

Conclusion

Based on existing international and local evidence , this is the first consensus guideline developed by gastroenterologists in Myanmar. Since *H. pylori* is the primary cause of stomach cancer, peptic ulcers, and their consequences, the first step is to properly diagnose and treat *H. pylori* infection. In order to prevent antibiotic resistance, individuals with *H. pylori* infection must have their infection successfully eradicated. Future study on P-CABs and the development of antibiotic sensitivity test are required. In Myanmar, this consensus will serve as a useful guide for clinicians in their day-to-day clinical work.

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